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  * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 10:13:46 ON 13 MAR 2002

=> fil .bec,canc
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.15       0.15

FILES 'MEDLINE, SCISEARCH, LIFESCI, BIOTECHDS, BIOSIS, EMBASE, HCAPLUS, NTIS,
       ESBIOBASE, BIOTECHNO, WPIDS, CANCERLIT' ENTERED AT 10:14:11 ON 13 MAR 2002
ALL COPYRIGHTS AND RESTRICTIONS APPLY.  SEE HELP USAGETERMS FOR DETAILS.

12 FILES IN THE FILE LIST

=> s hbx
FILE 'MEDLINE'
L1          255 HBX

FILE 'SCISEARCH'
L2          308 HBX

FILE 'LIFESCI'
L3          167 HBX

FILE 'BIOTECHDS'
L4            6 HBX

FILE 'BIOSIS'
L5          285 HBX

FILE 'EMBASE'
L6          217 HBX

FILE 'HCAPLUS'
L7          525 HBX

FILE 'NTIS'
L8           26 HBX

FILE 'ESBIOBASE'
L9          147 HBX

FILE 'BIOTECHNO'
L10         177 HBX

FILE 'WPIDS'
L11          10 HBX

FILE 'CANCERLIT'
L12         138 HBX

TOTAL FOR ALL FILES
L13        2261 HBX

=> s (hepatitis b virus or hbv)(8a)(inhibit? or treat?)
FILE 'MEDLINE'
         106059 HEPATITIS
         494945 B
```

```
        320536 VIRUS
         16904 HEPATITIS B VIRUS
                 (HEPATITIS(W)B(W)VIRUS)
          9818 HBV
        954842 INHIBIT?
       1713200 TREAT?
L14       1488 (HEPATITIS B VIRUS OR HBV)(8A)(INHIBIT? OR TREAT?)

FILE 'SCISEARCH'
         74037 HEPATITIS
        849990 B
        275166 VIRUS
         12733 HEPATITIS B VIRUS
                 (HEPATITIS(W)B(W)VIRUS)
          8027 HBV
        735729 INHIBIT?
       1230156 TREAT?
L15       1333 (HEPATITIS B VIRUS OR HBV)(8A)(INHIBIT? OR TREAT?)

FILE 'LIFESCI'
         18791 "HEPATITIS"
        170288 "B"
        161726 "VIRUS"
          7735 HEPATITIS B VIRUS
                 ("HEPATITIS"(W)"B"(W)"VIRUS")
          3906 HBV
        265968 INHIBIT?
        263743 TREAT?
L16        585 (HEPATITIS B VIRUS OR HBV)(8A)(INHIBIT? OR TREAT?)

FILE 'BIOTECHDS'
          3007 HEPATITIS
         30387 B
         31455 VIRUS
          1594 HEPATITIS B VIRUS
                 (HEPATITIS(W)B(W)VIRUS)
           401 HBV
         33482 INHIBIT?
         50878 TREAT?
L17          98 (HEPATITIS B VIRUS OR HBV)(8A)(INHIBIT? OR TREAT?)

FILE 'BIOSIS'
         90207 HEPATITIS
        589810 B
        438465 VIRUS
         22087 HEPATITIS B VIRUS
                 (HEPATITIS(W)B(W)VIRUS)
         10202 HBV
       1028043 INHIBIT?
       1511437 TREAT?
L18       1625 (HEPATITIS B VIRUS OR HBV)(8A)(INHIBIT? OR TREAT?)

FILE 'EMBASE'
         78894 "HEPATITIS"
        514081 "B"
        350839 "VIRUS"
         17154 HEPATITIS B VIRUS
                 ("HEPATITIS"(W)"B"(W)"VIRUS")
          8386 HBV
```

```
        847504 INHIBIT?
       1624138 TREAT?
L19       1436 (HEPATITIS B VIRUS OR HBV)(8A)(INHIBIT? OR TREAT?)

FILE 'HCAPLUS'
         33431 HEPATITIS
       1259026 B
        261813 VIRUS
          8425 HEPATITIS B VIRUS
                 (HEPATITIS(W)B(W)VIRUS)
          4767 HBV
       1466592 INHIBIT?
       2716782 TREAT?
L20       1268 (HEPATITIS B VIRUS OR HBV)(8A)(INHIBIT? OR TREAT?)

FILE 'NTIS'
          1178 HEPATITIS
         64605 B
          7171 VIRUS
           120 HEPATITIS B VIRUS
                 (HEPATITIS(W)B(W)VIRUS)
            76 HBV
         19313 INHIBIT?
        116790 TREAT?
L21          6 (HEPATITIS B VIRUS OR HBV)(8A)(INHIBIT? OR TREAT?)

FILE 'ESBIOBASE'
         15210 HEPATITIS
        194052 B
         69338 VIRUS
          3349 HEPATITIS B VIRUS
                 (HEPATITIS(W)B(W)VIRUS)
          2644 HBV
        279673 INHIBIT?
        344652 TREAT?
L22        481 (HEPATITIS B VIRUS OR HBV)(8A)(INHIBIT? OR TREAT?)

FILE 'BIOTECHNO'
         23233 HEPATITIS
        185240 B
        154983 VIRUS
          7201 HEPATITIS B VIRUS
                 (HEPATITIS(W)B(W)VIRUS)
          4246 HBV
        254665 INHIBIT?
        236388 TREAT?
L23        763 (HEPATITIS B VIRUS OR HBV)(8A)(INHIBIT? OR TREAT?)

FILE 'WPIDS'
          7720 HEPATITIS
        951966 B
         25774 VIRUS
          1005 HEPATITIS B VIRUS
                 (HEPATITIS(W)B(W)VIRUS)
           550 HBV
        173958 INHIBIT?
        761383 TREAT?
L24        289 (HEPATITIS B VIRUS OR HBV)(8A)(INHIBIT? OR TREAT?)
```

```
FILE 'CANCERLIT'
         19025 HEPATITIS
        126936 B
        108747 VIRUS
          4727 HEPATITIS B VIRUS
                 (HEPATITIS(W)B(W)VIRUS)
          3085 HBV
        210013 INHIBIT?
        462492 TREAT?
L25        700 (HEPATITIS B VIRUS OR HBV)(8A)(INHIBIT? OR TREAT?)

TOTAL FOR ALL FILES
L26      10072 (HEPATITIS B VIRUS OR HBV)(8A)(INHIBIT? OR TREAT?)

=> s l13 and l26
FILE 'MEDLINE'
L27          20 L1 AND L14

FILE 'SCISEARCH'
L28          20 L2 AND L15

FILE 'LIFESCI'
L29          15 L3 AND L16

FILE 'BIOTECHDS'
L30           1 L4 AND L17

FILE 'BIOSIS'
L31          22 L5 AND L18

FILE 'EMBASE'
L32          17 L6 AND L19

FILE 'HCAPLUS'
L33          58 L7 AND L20

FILE 'NTIS'
L34           0 L8 AND L21

FILE 'ESBIOBASE'
L35          16 L9 AND L22

FILE 'BIOTECHNO'
L36          14 L10 AND L23

FILE 'WPIDS'
L37           1 L11 AND L24

FILE 'CANCERLIT'
L38          12 L12 AND L25

TOTAL FOR ALL FILES
L39         196 L13 AND L26

=> s l13(10a)inhibit
FILE 'MEDLINE'
        110696 INHIBIT
L40          13 L1 (10A)INHIBIT
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FILE 'SCISEARCH'
         79129 INHIBIT
L41         10 L2 (10A)INHIBIT

FILE 'LIFESCI'
         38375 INHIBIT
L42         10 L3 (10A)INHIBIT

FILE 'BIOTECHDS'
          5079 INHIBIT
L43          0 L4 (10A)INHIBIT

FILE 'BIOSIS'
        118110 INHIBIT
L44         12 L5 (10A)INHIBIT

FILE 'EMBASE'
        107254 INHIBIT
L45         10 L6 (10A)INHIBIT

FILE 'HCAPLUS'
        159763 INHIBIT
L46         11 L7 (10A)INHIBIT

FILE 'NTIS'
          2808 INHIBIT
L47          0 L8 (10A)INHIBIT

FILE 'ESBIOBASE'
         37582 INHIBIT
L48          9 L9 (10A)INHIBIT

FILE 'BIOTECHNO'
         38905 INHIBIT
L49         10 L10(10A)INHIBIT

FILE 'WPIDS'
         88632 INHIBIT
L50          0 L11(10A)INHIBIT

FILE 'CANCERLIT'
         34066 INHIBIT
L51          8 L12(10A)INHIBIT

TOTAL FOR ALL FILES
L52         93 L13(10A) INHIBIT

=> s (139 or 152) not 1998-2002/py
FILE 'MEDLINE'
       1910647 1998-2002/PY
L53         10 (L27 OR L40) NOT 1998-2002/PY

FILE 'SCISEARCH'
       3931858 1998-2002/PY
L54          7 (L28 OR L41) NOT 1998-2002/PY

FILE 'LIFESCI'
        412069 1998-2002/PY
L55          6 (L29 OR L42) NOT 1998-2002/PY
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FILE 'BIOTECHDS'
         54587 1998-2002/PY
L56          0 (L30 OR L43) NOT 1998-2002/PY

FILE 'BIOSIS'
       2176551 1998-2002/PY
L57         10 (L31 OR L44) NOT 1998-2002/PY

FILE 'EMBASE'
       1766945 1998-2002/PY
L58          8 (L32 OR L45) NOT 1998-2002/PY

FILE 'HCAPLUS'
       3636686 1998-2002/PY
L59         26 (L33 OR L46) NOT 1998-2002/PY

FILE 'NTIS'
         64614 1998-2002/PY
L60          0 (L34 OR L47) NOT 1998-2002/PY

FILE 'ESBIOBASE'
       1154070 1998-2002/PY
L61          6 (L35 OR L48) NOT 1998-2002/PY

FILE 'BIOTECHNO'
        481303 1998-2002/PY
L62          8 (L36 OR L49) NOT 1998-2002/PY

FILE 'WPIDS'
       3115678 1998-2002/PY
L63          0 (L37 OR L50) NOT 1998-2002/PY

FILE 'CANCERLIT'
        289718 1998-2002/PY
L64          6 (L38 OR L51) NOT 1998-2002/PY

TOTAL FOR ALL FILES
L65         87 (L39 OR L52) NOT 1998-2002/PY

=> dup rem l65
PROCESSING COMPLETED FOR L65
L66          26 DUP REM L65 (61 DUPLICATES REMOVED)

=> d tot

L66  ANSWER 1 OF 26  HCAPLUS  COPYRIGHT 2002 ACS
TI   Ribozymes directed against hepatitis B virus
     RNA and the treatment of viral infection
SO   PCT Int. Appl., 34 pp.
     CODEN: PIXXD2
IN   Goldenberg, Tsvi; Yu, Mang; Welch, Peter J.; Barber, Jack R.
AN   1997:244380  HCAPLUS
DN   126:220698
     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
     ---------------   ----  --------      ---------------  --------
PI   WO 9708309         A2   19970306      WO 1996-US13975  19960829
     WO 9708309         A3   19970710
         W:  CA, JP
```

RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

L66 ANSWER 2 OF 26 MEDLINE DUPLICATE 1
TI Hepatitis B virus X protein and p53 tumor suppressor interactions in the modulation of apoptosis.
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1997 Dec 23) 94 (26) 14707-12.
Journal code: PV3; 7505876. ISSN: 0027-8424.
AU Elmore L W; Hancock A R; Chang S F; Wang X W; Chang S; Callahan C P; Geller D A; Will H; Harris C C
AN 1998070816 MEDLINE

L66 ANSWER 3 OF 26 MEDLINE DUPLICATE 2
TI **Inhibition** of hepatocellular carcinoma development in **hepatitis B virus** transfected mice by low dietary casein.
SO HEPATOLOGY, (1997 Nov) 26 (5) 1351-4.
Journal code: GBZ; 8302946. ISSN: 0270-9139.
AU Cheng Z; Hu J; King J; Jay G; Campbell T C
AN 1998026706 MEDLINE

L66 ANSWER 4 OF 26 HCAPLUS COPYRIGHT 2002 ACS
TI XAP2, a novel **hepatitis B virus** X-associated protein that **inhibits** X transactivation
SO Nucleic Acids Res. (1996), 24(23), 4741-4750
CODEN: NARHAD; ISSN: 0305-1048
AU Kuzhandaivelu, Nadarajan; Cong, Yu-Sheng; Inouye, Carla; Yang, Wen-Ming; Seto, Edward
AN 1997:6596 HCAPLUS
DN 126:55707

L66 ANSWER 5 OF 26 HCAPLUS COPYRIGHT 2002 ACS
TI Hepatitis B virus **HBx** protein activates transcription factor NF-.kappa.B by acting on multiple cytoplasmic inhibitors of rel-related proteins
SO J. Virol. (1996), 70(7), 4558-4566
CODEN: JOVIAM; ISSN: 0022-538X
AU Su, Fei; Schneider, Robert J.
AN 1996:358324 HCAPLUS
DN 125:55094

L66 ANSWER 6 OF 26 MEDLINE DUPLICATE 3
TI **Inhibition** of **hepatitis-B-virus** core promoter by p53: implications for carcinogenesis in hepatocytes.
SO INTERNATIONAL JOURNAL OF CANCER, (1996 Sep 17) 67 (6) 892-7.
Journal code: GQU; 0042124. ISSN: 0020-7136.
AU Uchida T; Takahashi K; Tatsuno K; Dhingra U; Eliason J F
AN 96421947 MEDLINE

L66 ANSWER 7 OF 26 MEDLINE DUPLICATE 4
TI The effect of **hepatitis B virus** X gene expression on response to growth **inhibition** by transforming growth factor-beta 1.
SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1996 May 24) 222 (3) 770-3.
Journal code: 9Y8; 0372516. ISSN: 0006-291X.
AU Oshikawa O; Tamura S; Kawata S; Ito N; Tsushima H; Kiso S; Matsuda Y; Yamada A; Tamai S; Matsuzawa Y
AN 96244576 MEDLINE

L66 ANSWER 8 OF 26 HCAPLUS COPYRIGHT 2002 ACS
TI Hepatitis B virus pX activates NF-.kappa.B-dependent transcription through a Raf-independent pathway
SO J. Virol. (1996), 70(1), 641-6
CODEN: JOVIAM; ISSN: 0022-538X
AU Chirillo, Paolo; Falco, Mirella; Puri, Pier Lorenzo; Artini, Marco; Balsano, Clara; Levrero, Massimo; Natoli, Gioacchino
AN 1995:990553 HCAPLUS
DN 124:52376

L66 ANSWER 9 OF 26 MEDLINE DUPLICATE 5
TI In vivo **inhibition** of **hepatitis B virus** gene expression by antisense phosphorothioate oligonucleotides.
SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1996 Jan 5) 218 (1) 217-23.
Journal code: 9Y8; 0372516. ISSN: 0006-291X.
AU Moriya K; Matsukura M; Kurokawa K; Koike K
AN 96136303 MEDLINE

L66 ANSWER 10 OF 26 HCAPLUS COPYRIGHT 2002 ACS
TI Antiviral and anti-proliferative activities of .alpha. interferons in experimental hepatitis B virus infections
SO Antiviral Ther. (1996), 1(Suppl. 4, Therapies for Viral Hepatitis), 64-70
CODEN: ANTHFA; ISSN: 1359-6535
AU Gangemi, J. David; Korba, Brent; Tennant, Bud; Ueda, Hiroyuki; Jay, Gilbert
AN 1997:228421 HCAPLUS
DN 126:262824

L66 ANSWER 11 OF 26 HCAPLUS COPYRIGHT 2002 ACS
TI Hepatitis B virus (HBV) interacts with cellular DNA repair processes
SO PCT Int. Appl., 44 pp.
CODEN: PIXXD2
IN Butel, Janet S.; Lee, Teh-Hsiu; Elledge, Stephen J.
AN 1995:761653 HCAPLUS
DN 123:311748

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9510288	A1	19950420	WO 1994-US11451	19941012
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9479725	A1	19950504	AU 1994-79725	19941012

L66 ANSWER 12 OF 26 HCAPLUS COPYRIGHT 2002 ACS
TI X-gene product antagonizes the p53-mediated **inhibition** of **hepatitis B virus** replication through regulation of the pregenomic/core promoter
SO J. Biol. Chem. (1995), 270(52), 31405-12
CODEN: JBCHA3; ISSN: 0021-9258
AU Lee, Hyunsook; Lee, Young-Ho; Huh, Yun-Sil; Moon, Hongmo; Yun, Yungdae
AN 1996:29140 HCAPLUS
DN 124:108778

L66 ANSWER 13 OF 26 MEDLINE DUPLICATE 6
TI Abrogation of p53-induced apoptosis by the hepatitis B virus X gene.
SO CANCER RESEARCH, (1995 Dec 15) 55 (24) 6012-6.
Journal code: CNF; 2984705R. ISSN: 0008-5472.

AU Wang X W; Gibson M K; Vermeulen W; Yeh H; Forrester K; Sturzbecher H W; Hoeijmakers J H; Harris C C
AN 96105011 MEDLINE

L66 ANSWER 14 OF 26 HCAPLUS COPYRIGHT 2002 ACS
TI Expression of the terminal protein region of **hepatitis B virus inhibits** cellular responses to interferons .alpha. and .gamma. and double-stranded RNA. [Erratum to document cited in CA114:205330]
SO Proc. Natl. Acad. Sci. U. S. A. (1995), 92(8), 3632
CODEN: PNASA6; ISSN: 0027-8424
AU Foster, Graham R.; Ackrill, Andrew M.; Goldin, Robert D.; Kerr, Ian M.; Thomas, Howard C.; Stark, George R.
AN 1995:510542 HCAPLUS
DN 123:7696

L66 ANSWER 15 OF 26 MEDLINE DUPLICATE 7
TI Direct interaction of the **hepatitis B virus HBx** protein with p53 leads to **inhibition** by **HBx** of p53 response element-directed transactivation.
SO JOURNAL OF VIROLOGY, (1995 Mar) 69 (3) 1851-9.
Journal code: KCV; 0113724. ISSN: 0022-538X.
AU Truant R; Antunovic J; Greenblatt J; Prives C; Cromlish J A
AN 95156618 MEDLINE

L66 ANSWER 16 OF 26 HCAPLUS COPYRIGHT 2002 ACS
TI Disruption of the function of tumor-suppressor gene p53 by the hepatitis B virus X protein and hepatocarcinogenesis
SO J. Cancer Res. Clin. Oncol. (1995), 121(9/10), 593-601
CODEN: JCROD7; ISSN: 0171-5216
AU Takada, Shinako; Tsuchida, Nobuo; Kobayashi, Midori; Koike, Katsuro
AN 1996:4128 HCAPLUS
DN 124:83486

L66 ANSWER 17 OF 26 HCAPLUS COPYRIGHT 2002 ACS
TI Putative secondary structure of human hepatitis B viral X mRNA
SO J. Biochem. Mol. Biol. (1995), 28(6), 509-14
CODEN: JBMBE5; ISSN: 1225-8687
AU Kim, Hadong; Choi, Yoon Chul; Lee, Bum Yong; Junn, Eunsung; Ahn, Jeongkeun; Kang, Changwon; Park, Inwon
AN 1995:1007863 HCAPLUS
DN 124:110002

L66 ANSWER 18 OF 26 HCAPLUS COPYRIGHT 2002 ACS
TI **Inhibition** of **hepatitis B virus** X protein gene expression by its antisense RNA in E. coli
SO Wuhan Daxue Xuebao, Ziran Kexueban (1995), 41(4), 475-81
CODEN: WTHPDI; ISSN: 0253-9888
AU Yang, Jianqi; Zhang, Xiyuan; Li, Wenxin; Zhang, Xiaogang; Wang, Ping
AN 1996:60066 HCAPLUS
DN 124:137017

L66 ANSWER 19 OF 26 MEDLINE DUPLICATE 8
TI **Hepatitis B virus** X protein **inhibits** p53 sequence-specific DNA binding, transcriptional activity, and association with transcription factor ERCC3.
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1994 Mar 15) 91 (6) 2230-4.
Journal code: PV3; 7505876. ISSN: 0027-8424.

AU Wang X W; Forrester K; Yeh H; Feitelson M A; Gu J R; Harris C C
AN 94181566 MEDLINE

L66 ANSWER 20 OF 26 HCAPLUS COPYRIGHT 2002 ACS
TI Interaction of hepatitis B virus X protein with a serine protease, tryptase TL2 as an inhibitor
SO Oncogene (1994), 9(2), 341-8
CODEN: ONCNES; ISSN: 0950-9232
AU Takada, Shinako; Kido, Hiroshi; Fukutomi, Aiko; Mori, Takeshi; Koike, Katsuro
AN 1994:211292 HCAPLUS
DN 120:211292

L66 ANSWER 21 OF 26 MEDLINE DUPLICATE 9
TI Transactivation of human hepatitis B virus X protein, HBx, operates through a mechanism distinct from protein kinase C and okadaic acid activation pathways.
SO VIROLOGY, (1994 Feb 15) 199 (1) 243-6.
Journal code: XEA; 0110674. ISSN: 0042-6822.
AU Murakami S; Cheong J; Ohno S; Matsushima K; Kaneko S
AN 94160577 MEDLINE

L66 ANSWER 22 OF 26 HCAPLUS COPYRIGHT 2002 ACS
TI Methods for using recombinant bacteria to identify and produce medically important agents
SO PCT Int. Appl., 61 pp.
CODEN: PIXXD2
IN Block, Timothy M.; Grafstrom, Robert H.
AN 1993:206927 HCAPLUS
DN 118:206927

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9213972	A1	19920820	WO 1992-US1188	19920211
W: JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE				
US 5532124	A	19960702	US 1993-98313	19931006

L66 ANSWER 23 OF 26 MEDLINE DUPLICATE 10
TI **Hepatitis B virus** transactivator MHBst: activation of NF-kappa B, selective **inhibition** by antioxidants and integral membrane localization.
SO EMBO JOURNAL, (1992 Aug) 11 (8) 2991-3001.
Journal code: EMB; 8208664. ISSN: 0261-4189.
AU Meyer M; Caselmann W H; Schluter V; Schreck R; Hofschneider P H; Baeuerle P A
AN 92347334 MEDLINE

L66 ANSWER 24 OF 26 HCAPLUS COPYRIGHT 2002 ACS
TI Expression of the terminal protein region of **hepatitis B virus inhibits** cellular responses to interferons .alpha. and .gamma. and double-stranded RNA
SO Proc. Natl. Acad. Sci. U. S. A. (1991), 88(7), 2888-92
CODEN: PNASA6; ISSN: 0027-8424
AU Foster, Graham R.; Ackrill, Andrew M.; Goldin, Robert D.; Kerr, Ian M.; Thomas, Howard C.; Stark, George R.
AN 1991:205330 HCAPLUS
DN 114:205330

L66 ANSWER 25 OF 26 HCAPLUS COPYRIGHT 2002 ACS

TI X protein of **hepatitis B virus** resembles a serine protease **inhibitor**
SO Jpn. J. Cancer Res. (1990), 81(12), 1191-4
CODEN: JJCREP; ISSN: 0910-5050
AU Takada, Shinako; Koike, Katsuro
AN 1991:138258 HCAPLUS
DN 114:138258

L66 ANSWER 26 OF 26 HCAPLUS COPYRIGHT 2002 ACS
TI trans-Activation of viral enhancers by the hepatitis B virus X protein
SO J. Virol. (1988), 62(2), 427-34
CODEN: JOVIAM; ISSN: 0022-538X
AU Spandau, Dan F.; Lee, Chao Hung
AN 1988:88696 HCAPLUS
DN 108:88696

=> d ab tot

L66 ANSWER 1 OF 26 HCAPLUS COPYRIGHT 2002 ACS
AB Ribozymes useful in the **treatment** or prophylaxis of **hepatitis B virus** (**HBV**) infection and expression constructs for their delivery are described. Selection of cleavage sites and the design and construction of ribozyme expression vectors is described. Characterization of the in vitro catalytic properties of ribozymes is also described.

L66 ANSWER 2 OF 26 MEDLINE DUPLICATE 1
AB We have reported previously that the hepatitis B virus oncoprotein, **HBx**, can bind to the C terminus of p53 and **inhibit** several critical p53-mediated cellular processes, including DNA sequence-specific binding, transcriptional transactivation, and apoptosis. Recognizing the importance of p53-mediated apoptosis for maintaining homeostasis and preventing neoplastic transformation, here we further examine the physical interaction between HBx and p53 as well as the functional consequences of this association. In vitro binding studies indicate that the ayw and adr viral subtypes of HBx bind similar amounts of glutathione S-transferase-p53 with the distal C terminus of HBx (from residues 111 to 154) being critical for this interaction. Using a microinjection technique, we show that this same C-terminal region of HBx is necessary for sequestering p53 in the cytoplasm and abrogating p53-mediated apoptosis. The transcriptional transactivation domain of HBx also maps to its C terminus; however, a comparison of the ability of full-length and truncated HBx protein to abrogate p53-induced apoptosis versus transactivate simian virus 40- or human nitric oxide synthase-2 promoter-driven reporter constructs indicates that these two functional properties are distinct and thus may contribute to hepatocarcinogenesis differently. Collectively, our data indicate that the distal C-terminal domain of HBx, independent of its transactivation activity, complexes with p53 in the cytoplasm, partially preventing its nuclear entry and ability to induce apoptosis. These pathobiological effects of HBx may contribute to the early stages of hepatocellular carcinogenesis.

L66 ANSWER 3 OF 26 MEDLINE DUPLICATE 2
AB In a comprehensive human ecological study, primary liver cancer has been shown to be highly significantly associated with 1) the prevalence of persistent infection with hepatitis B virus (HBV) and 2) plasma cholesterol concentrations that are, in turn, associated with the consumption of animal based foods. In rat studies, aflatoxin-induced

hepatocellular carcinoma is substantially prevented by decreasing the intake of animal based protein (casein), a hypercholesterolemic nutrient. Thus the development of primary liver cancer associated with persistent HBV infection or with aflatoxin exposure may be controlled by reduced intake of animal-based proteins. Transgenic mice transfected with an HBV gene fragment containing the viral transactivator of hepatis B virus, **HBx**, which induces the formation of hepatocellular carcinoma, were used to examine the ability of dietary casein to modify tumor formation. Reducing the concentration of dietary casein to 6% from the traditional level of 22% markedly inhibited (by 75%) hepatic tumor formation in these transgenic mice. Tumor development also was substantially altered by interchanging dietary casein concentration well after tumor development had begun (at 8 months), increasing by 173% from the expected yield when casein intake was increased and decreasing by 99% when casein was reduced. These findings suggest that the development of liver tumor formation among individuals persistently infected with HBV may be controlled by minimizing or eliminating the intake of animal protein-based foods.

L66 ANSWER 4 OF 26 HCAPLUS COPYRIGHT 2002 ACS

AB The hepatitis B virus X protein is a promiscuous transcriptional transactivator. Transactivation by the X protein is most likely mediated through binding to different cellular factors. Using the yeast two-hybrid method, the authors have isolated a clone that encodes a novel X-assocd. cellular protein: XAP2. X and XAP2 interactions also occur in vitro. Antiserum raised against XAP2 recognizes a cytoplasmic protein with an apparent mol. mass of 36 kDa. The interaction between X and XAP2 requires a small region on X contg. amino acids 13-26. From Northern blot analyses, XAP2 is ubiquitously expressed in both liver-derived and non-liver-derived cell lines as well as in normal non-liver tissues. In contrast, XAP2 is expressed in very low level in the normal human liver. In transfection assays, overexpression of XAP2 abolished transactivation by the X protein. Based on these results, the authors suggest that the XAP2 is an important cellular neg. regulator of the X protein, and that X-XAP2 interaction may play a role in HBV pathol.

L66 ANSWER 5 OF 26 HCAPLUS COPYRIGHT 2002 ACS

AB The **HBx** protein is a small polypeptide encoded by mammalian hepadnaviruses that is essential for viral infectivity and is thought to play a role in development of hepatocellular carcinoma during chronic hepatitis B virus infection. **HBx** is a transactivator that stimulates Ras signal transduction pathways in the cytoplasm and certain transcription elements in the nucleus. To better understand the activities of **HBx** protein and its mechanism of action, the authors have explored the manner by which **HBx** activates the transcription factor NF-.kappa.B during transient expression. The authors show that **HBx** induces prolonged formation, in a Ras-dependent manner, of transcriptionally active NF-.kappa.B DNA-binding complexes, which make up the family of Rel-related proteins, p50, p52, RelA, and c-Rel. **HBx** was found to activate NF-.kappa.B through two distinct cytoplasmic pathways by acting on both the 37-kDa I.kappa.B.alpha. inhibitor and the 105-kDa NF-.kappa.B1 precursor inhibitor protein, known as p105. **HBx** induces phosphorylation of I.kappa.B.alpha., a three- to fourfold redn. in I.kappa.B.alpha. stability, and concomitant nuclear accumulation of NF-.kappa.B DNA-binding complexes, similar to that reported for human T-cell leukemia virus type 1 Tax protein. In addn., **HBx** mediates a striking redn. in cytoplasmic p105 NF-.kappa.B1 inhibitor and p50 protein levels and release of RelA protein that was sequestered by the p105 inhibitor, concomitant with nuclear accumulation of NF-.kappa.B complexes. **HBx**

mediated only a slight redn. in the cytoplasmic levels of NF-.kappa.B2 p100 protein, an addnl. precursor inhibitor of NF-.kappa.B, which is thought to be less efficiently processed or less responsive to release of NF-.kappa.B. No evidence was found for **HBx** activation of NF-.kappa.B by targeting acidic sphingomyelinase-controlled pathways. Studies also suggest that stimulation of NF-.kappa.B by **HBx** does not involve activation of Ras via the neutral sphingomyelin-ceramide pathway. Thus **HBx** protein is shown to activate the NF-.kappa.B family of Rel-related proteins by acting on two distinct NF-.kappa.B cytoplasmic inhibitors.

L66 ANSWER 6 OF 26 MEDLINE DUPLICATE 3

AB The incidence of hepatocellular carcinoma (HCC) is particularly high in regions of Asia and sub-Saharan Africa where rates of infection with human hepatitis-B virus (HBV) and aflatoxin-B1 contamination of food are high. In HCC tumors occurring in inhabitants of these regions, a G-to-T mutation frequently occurs at position 249 of the tumor-suppressor gene p53. This suggests that HBV and p53 mutation may collaborate in the carcinogenic process in liver. We have examined the effect of the HBV protein **HBX** in HCC lines with exogenous wild-type p53 or mutated p53 on transactivation of 2 different reporter genes. Transfection of HCC lines with wild-type p53 and a reporter with the promoter from the p53-responsive gene WAF1/p21 resulted in a high level of expression, as expected. When cells were co-transfected with a reporter gene driven by the HBV core promoter and with the **HBX** gene, expression was enhanced in the Hep 3B, HLE, PLC/PRF/5 and HuH 7 lines, but not in the HuH 1 line. Co-transfection of the reporter with a plasmid containing wild-type p53 resulted in significant **inhibition** of the **HBV** core promoter in all of the lines, whereas the mutated p53 gene had no effect. Our results indicate that wild-type p53 can **inhibit** transcription from the **HBV** core promoter. In similar experiments, both **HBX** and p53 were co-transfected into HCC lines with the WAF1/p21 reporter gene. **HBX** inhibited p53-induced expression in 4 of the 6 lines (Hep 3B, HuH 1, HuH 7 and HLE), there was no effect in one line (HLF), and enhancement was evident in PLC/PRF/5. Our results indicate that inhibition of p53 transcriptional activity by **HBX** does occur in HCC, but is highly cell-context-dependent. **Inhibition** of transcription from the **HBV** core promoter by wild-type p53 appears to be more universal, and may represent a mechanism by which wild-type p53 can protect against the carcinogenic process in liver.

L66 ANSWER 7 OF 26 MEDLINE DUPLICATE 4

AB Hepatitis B virus X protein (**HBx** protein), which seems to be involved in hepatocarcinogenesis, was studied for its effect on cell growth regulation. We examined the response to growth inhibition of transforming growth factor beta 1 (TGF-beta 1) in **HBx** gene-introduced cells. **HBx** gene in pRc/CMV was transfected to mink lung epithelial cells (Mv1Lu cells) and a stable transformant was obtained. The inhibition rates of [3H] thymidine incorporation by addition of TGF-beta 1 (0.08 ng/ml) to parent cells and pRc/CMV-transfected cells were 34% and 26%, respectively. However, the inhibition rates in the **HBx** gene-transfected cells were 3-8%. The amount of TGF-beta type II receptor on the surface of **HBx** gene-transfected cells was about half of that on the parent or pRc/CMV-transfected cells. Our results indicated that expression of **HBx** gene reduces the response to growth inhibition by TGF-beta 1.

L66 ANSWER 8 OF 26 HCAPLUS COPYRIGHT 2002 ACS

AB In this study, the authors characterized the mol. events involved in the activation of the ubiquitous transcription factor NF-.kappa.B by the viral transactivator pX. PX expression in HeLa cells dets. a manyfold increase in NF-.kappa.B-dependent transcription, which is assocd. with an increase in p50/p65 heterodimer DNA-binding activity. Since the I.kappa.B-.alpha. inhibitory subunit proteolytic degrdn., which follows its phosphorylation/modification, is a key event in NF-.kappa.B activation by different stimuli (such as growth factors, phorbol esters, tumor necrosis factor, UV irradn., and oxygen radicals), the authors investigated pX effects on I.kappa.B-.alpha., as well as the possible involvement of known signaling pathways in pX-induced NF-.kappa.B-dependent transcription. The authors obsd. that although pX had no direct effect on p50 or p65, it was able to restore the I.kappa.B-.alpha.-suppressed p50/p65 activity. More directly, the stable expression of pX in HeLa cells resulted in reduced levels of I.kappa.B-.alpha. in the cytoplasm. Pretreatment of the cells with H 7, calphostin C, tyrphostin 25, or N-acetylcysteine did not impair the effects of pX on NF-.kappa.B, thus ruling out the involvement of protein kinase C, tyrosine kinases, and oxygen radicals. Finally, while most of the known NF-.kappa.B-activating agents converge on Raf-1 protein kinase, when Raf-1 activity is blocked by overexpression of a dominant neg. mutant, the effects of pX on NF-.kappa.B are not impaired. Thus, the authors suggest that although pX is able to activate the Ras/Raf-1-signaling pathway, it triggers NF-.kappa.B activation by an as yet unidentified Raf-1-independent pathway.

L66 ANSWER 9 OF 26 MEDLINE DUPLICATE 5
AB While an important goal of treatment for hepatitis B is to prevent the development of hepatocellular carcinoma, there has been no effective therapy for it. Antisense oligodeoxynucleotide **treatment** could in principle **inhibit hepatitis B virus** gene expression and suppress tumor development. We used a mouse model for hepatocellular carcinoma, which is transgenic for the hepatitis B virus **HBx** gene, to study antisense phosphorothioate oligodeoxynucleotides. Among 2 series of sense and antisense oligodeoxynucleotides, only antisense sequences covering the initiation codon of the **HBx** gene effectively inhibited the expression of the **HBx** gene in the liver. Intraperitoneal injection of this antisense oligodeoxynucleotide thrice a week for 8 weeks resulted in the prevention of preneoplastic lesion development in the liver without inflammation in the liver or developmental disturbance of the mice. Antisense phosphorothioate oligodeoxynucleotides can **inhibit** the expression of a **hepatitis B virus** gene and may be a promising method for the prevention of hepatocellular carcinoma in hepatitis B virus infection.

L66 ANSWER 10 OF 26 HCAPLUS COPYRIGHT 2002 ACS
AB A review with 18 refs. Interferon-.alpha. (IFN-.alpha.) has been the drug of choice for the **treatment** of chronic **hepatitis B virus** (**HBV**) infections for the past 20 yr, yet little more is known about the mechanism of action of this cytokine today than in 1975 when some of the first trials were performed. The lack of knowledge concerning the activity of interferon is, in part, a consequence of the absence of exptl. models with which to study antiviral and immune mechanisms. This problem is intensified by the species specificity of human IFN-.alpha.. In contrast to the classical IFN-.alpha. subtypes currently in use, hybrid forms, consisting of multiple IFN-.alpha. subtypes, are active in various animals and can provide a unique opportunity to study the cellular mechanism(s) of interferon action in chronic HBV infections. Here the authors discuss the

antiviral, immunomodulatory, and anti-proliferative activities of one human IFN-.alpha. hybrid (IFN-.alpha. B/D) in hepatocytes productively infected with HBV, woodchucks chronically infected with woodchuck hepatitis virus, and mice transfected with the **HBx** oncogene.

L66 ANSWER 11 OF 26 HCAPLUS COPYRIGHT 2002 ACS
AB Viral disease is treated in an animal or human by interfering with the interaction of the viral protein with a DNA repair complex in the animal or human host to be treated. Specific examples include **inhibition** of the interaction of the X protein from **HBV** and the XAP-1 protein of the DNA repair complex. The method can also be used for the treatment of cancer secondary to viral infection. A nucleic acid sequence encoding the XAP-1 protein and the amino acid sequence of the XAP-1 protein are presented. Antibodies to the protein can be used for diagnostic purposes and the XAP-1 gene can be used as the object of screening assays to detect genetic alterations. The XAP-1 protein was identified by use of a yeast 2-hybrid system (Fields and Song, 1989) in which the bait component was a plasmid expressing a GAL4 DNA-binding domain fused to the X protein, and the prey component was a plasmid contg. the GAL4 transcription activator domain DNA fused to host library cDNA m immortalized human lymphocytes. Interaction between bait and prey plasmids led to transcriptional activation of a reporter gene (lacZ).

L66 ANSWER 12 OF 26 HCAPLUS COPYRIGHT 2002 ACS
AB The glutathione S-transferase column retention method and far Western anal. were employed to find a phys. assocn. between tumor suppressor p53 and the hepatitis B virus X-gene product, which led to study of the function of the obsd. interaction in relation to viral propagation. In a cell culture-based in vitro replication system, expression of p53 resulted in dramatic inhibition of viral replication, and this inhibition was relieved by coexpression of the X-gene product in a dose-dependent manner. Furthermore, the activity of pregenomic/core promoter, responsible for the synthesis of pregenomic RNA, was almost completely inhibited upon expression of p53, and as in the replication assay, the inhibition was rescued by the coexpression of the X-gene product in a dose-dependent manner. Based on these results, the ratio of X-gene product to p53 is proposed to be an important factor detg. the fate of viral replication through modulation of the pregenomic/core promoter.

L66 ANSWER 13 OF 26 MEDLINE DUPLICATE 6
AB The p53 tumor suppressor gene product is a transcriptional transactivator and a potent apoptotic inducer. The fact that many of the DNA tumor virus oncoproteins bind to p53 and affect these p53 functions indicates that this interaction is an important step in oncogenic transformation. We and others have recently demonstrated that the hepatitis B virus oncoprotein, **HBx**, can form a complex with p53 and **inhibit** its DNA consensus sequence binding and transcriptional transactivator activity. Using a microinjection technique, we report here that HBx efficiently blocks p53-mediated apoptosis and describe the results of studies exploring two possible mechanisms of HBx action. First, inhibition of apoptosis may be a consequence of the failure of p53, in the presence of HBx, to upregulate genes, such as p21WAF1, Bax, or Fas, that are involved in the apoptotic pathway. Data consistent with this hypothesis include HBx reduction of p53-mediated p21WAF1 expression. Alternatively, HBx could affect p53 binding to the TFIIH transcription-nucleotide excision repair complex as HBx binds to the COOH terminus of p53 and inhibits its binding to XPB or XPD. Binding of p53 to these constituents of the core TFIIH is a process that may be involved in apoptosis. Because the HBx gene is frequently integrated into the genome of hepatocellular carcinoma cells,

inhibition of p53-mediated apoptosis by HBx may provide a clonal selective advantage for hepatocytes expressing this integrated viral gene during the early stages of human liver carcinogenesis.

L66 ANSWER 14 OF 26 HCAPLUS COPYRIGHT 2002 ACS
AB The errors were not reflected in the abstr. or the index entries.

L66 ANSWER 15 OF 26 MEDLINE DUPLICATE 7
AB Hepatitis B virus is a major risk factor in human hepatocellular carcinomas. We have used protein affinity chromatography to show that the 17-kDa hepatitis B virus gene product, **HBx**, binds directly to the human tumor suppressor gene product, p53. Interaction of **HBx** with p53 did not prevent p53 from specifically binding DNA. Instead, **HBx** enhanced p53's oligomerization state on a DNA oligonucleotide containing a p53 response element. Optimal binding of **HBx** to p53 required intact p53, but weaker binding to both the N-terminal activation domain of p53 and a protein fragment containing the C-terminal DNA-binding and oligomerization domains of p53 was observed. In transient transfection experiments with human Calu-6 cells, **HBx** inhibited transactivation by p53 of a reporter gene containing a p53 response element. Also, **HBx** inhibited p53-stimulated transcription in vitro even when added to the reaction mixture after the formation of the preinitiation complex. Interaction of **HBx** with p53 did not prevent the activation domain of p53 from binding two general initiation factors, the TATA-box binding protein subunit of TFIID and the p62 subunit of TFIIH. To explain these results, we propose that localization of **HBx** to a promoter by interaction with DNA-bound p53 enables a repression domain in **HBx** to directly contact the basal transcription machinery and thereby repress transcription.

L66 ANSWER 16 OF 26 HCAPLUS COPYRIGHT 2002 ACS
AB The X gene of the hepatitis B virus codes for a small basic protein and is able to transactivate viral and cellular genes, although the X protein exhibits no DNA-binding activity. The mechanism of transactivation by X protein has been suggested to be via protein-protein interaction(s). The authors first demonstrated that X protein had amino acid sequences homologous to the functionally essential domain of Kunitz-type serine protease inhibitors and that those sequences were indispensable for the transactivation function. The authors demonstrated that X protein exhibited an inhibitor activity against hepatic serine proteases, and subsequently found that the protein activated X gene transcription in HepG2 cells and that the X responsive element was localized in the minimal promoter of the X gene. In contrast, the tumor-suppressor gene p53, but not mutant p53, remarkably reduced transcription from the minimal promoter. This p53 repression on the X gene promoter was cancelled by X gene co-expression, probably indicating that the X protein disrupts the p53 tumor suppressor function in the nucleus. All data suggest that X protein leads to transactivation of cellular oncogenes by preventing an interaction between p53 and cellular transcription factor(s) consisting of the basal transcriptional machinery.

L66 ANSWER 17 OF 26 HCAPLUS COPYRIGHT 2002 ACS
AB A putative secondary structure of the mRNA for the human hepatitis B virus (HBV) X gene is proposed based on not only chem. and enzymic detn. of its single- and double-stranded regions but also selection by the computer program MFOLD for energy min. conformation under the constraints that the exptl. detd. nucleotides were forced or prohibited to base pair. An RNA of 536 nucleotides including the 461-nucleotide HBV X mRNA sequence was synthesized in vitro by the phage T7 RNA polymerase transcription. The

thermally renatured transcripts were subjected to chem. modifications with dimethylsulfate and kethoxal and enzymic hydrolysis with single strand-specific RNase T1 and double strand-specific RNase V1, sep. The sites of modification and cleavage were detected by reverse transcriptase extension of 4 different primers. Many nucleotides could be assigned with high confidence, twenty in double-stranded and thirty-seven in single-stranded regions. These nucleotides were forced and prohibited resp., to base pair in running the recursive RNA folding program MFOLD. The results suggest that 6 different regions (5 within X mRNA) of 14.apprx.23 nucleotides are single-stranded. This putative structure provides a good working model and suggests potential target sites for antisense and ribozyme **inhibitors** and hybridization probes for the **HBV** X mRNA.

L66 ANSWER 18 OF 26 HCAPLUS COPYRIGHT 2002 ACS
AB The entire HBV X gene DNA sequence was placed under control of the PL promoter of expression plasmids pBV-221 and pBV-220. The result showed that recombinant plasmids pBV-**HBX**(+) and pBV-**HBX**(-) were constructed successfully. In pBV-**HBX**(+), HBV X gene was cloned and could express X protein. In pBV-**HBX**(-), the X gene's direction was opposite and this plasmid could only transcribe the antisense RNA of HBV X gene. With the two plasmids, plasmid pEX.AN-**HBX** transcribed HBV X gene mRNA and constructed antisense RNA at same time. A prokaryotic expression system transformed with the above plasmids, successfully expressed HBV X protein in E. coli DH4.alpha.. Expression of protein X was inhibited by antisense RNA in E. coli DH5.alpha..

L66 ANSWER 19 OF 26 MEDLINE DUPLICATE 8
AB Chronic active hepatitis caused by infection with hepatitis B virus, a DNA virus, is a major risk factor for human hepatocellular carcinoma. Since the oncogenicity of several DNA viruses is dependent on the interaction of their viral oncoproteins with cellular tumor-suppressor gene products, we investigated the interaction between hepatitis B virus X protein (**HBX**) and human wild-type p53 protein. **HBX** complexes with the wild-type p53 protein and inhibits its sequence-specific DNA binding in vitro. **HBX** expression also inhibits p53-mediated transcriptional activation in vivo and the in vitro association of p53 and ERCC3, a general transcription factor involved in nucleotide excision repair. Therefore, **HBX** may affect a wide range of p53 functions and contribute to the molecular pathogenesis of human hepatocellular carcinoma.

L66 ANSWER 20 OF 26 HCAPLUS COPYRIGHT 2002 ACS
AB X protein of hepatitis B virus (HBV) transactivates transcription of various viral and cellular genes. It has been suggested that X protein plays a major role in hepatocarcinogenesis by HBV. The protein possesses amino acid sequence homol. to the functionally essential domain of Kunitz-type serine protease inhibitors. This Kunitz domain-like sequence in X protein is indispensable for the transactivation function. To clarify whether X protein has a serine protease inhibitor activity, a search was made for serine proteases which interact with, but not degrade X protein. Tryptase TL2, one of serine proteases in hepatic cells, was found to directly interact with X protein without degrdn. Moreover, the activities of tryptase TL2 and an analogous protease were substantially inhibited by X protein. These results suggest that transactivation function of X protein is exerted by modulation of the hepatic serine protease activity, giving rise to quant. or qual. change of cellular transcription factor(s) through protection from proteolytic degrdn. and/or

suppression of processing.

L66 ANSWER 21 OF 26 MEDLINE DUPLICATE 9
AB Human hepatitis B virus (HBV) X protein, HBx, transactivates virus and host genes through a wide variety of cis-elements. Expression of HBx is controlled by HBV enhancer 1 (Enh1). Both Enh1 and the core sequence of Enh1, which consists of an AP-1 related site (cFAP1) and a C stretch, respond to HBx and a phorbol ester (TPA). Biochemical pathways of the responses to HBx and TPA are still controversial. We therefore asked whether HBx and TPA stimulate Enh1 core activity through a common process. Protein kinase C (PKC) inhibitors, H-7 and staurosporin, did not **inhibit HBx** transactivation at concentrations sufficient to abolish the TPA effects in HepG2 cells. Although HBx transactivation synergized independently with TPA or a phosphoprotein phosphatase inhibitor, okadaic acid (OA), the PKC inhibitors eliminated only the TPA contribution. HBx transactivation required both the cFAP1 and the C stretch of the Enh1 core region; however, mutations in either or both of the two cis-elements demonstrated that TPA augmentation required only cFAP1. These results imply that HBx transactivation operates through a mechanism distinct from the PKC and OA activation pathways.

L66 ANSWER 22 OF 26 HCAPLUS COPYRIGHT 2002 ACS
AB Microorganisms modified such that their growth in selective media is dependent upon the inhibition of a medically important target function are provided and utilized in methods for the screening of potential medically important compds. Transgenic Escherichia coli contg. an HIV protease gene and a modified tetracycline resistance gene were prepd. The modified tetracycline resistance gene encoded a protein contg. a peptide sequence susceptible to digestion by HIV protease. In selection medium contg. tetracycline, the transgenic E. coli cannot grow unless expression of the HIV protease gene is inhibited or repressed or unless an inhibitor of the HIV protease is present. The transgenic E. coli was able to grow in the presence of tetracycline when pepstatin A was added to the culture. This transformant may be used to identify previously unknown HIV protease inhibitors.

L66 ANSWER 23 OF 26 MEDLINE DUPLICATE 10
AB C-terminal truncation of the middle surface antigen from hepatitis B virus (MHBs) gives rise to a novel transactivating protein, called MHBst. In this study we show that MHBst like the **HBx** protein of HBV, can cause nuclear appearance of NF-kappa B DNA binding activity and induce various kappa B-controlled reporter genes. While an inhibitor of protein kinase C could not block gene induction by MHBst, the antioxidants N-acetyl-L-cysteine (NAC) and pyrrolidine dithiocarbamate (PDTC) could potently suppress transactivation at mM and microM concentrations, respectively. Also, kappa B-dependent gene induction by the transactivator **HBx** was blocked. The effects were selective because PDTC did not interfere with MHBst and **HBx**-induced activation of the c-fos promoter/enhancer, nor with the basal activity of several other reporter genes lacking functional NF-kappa B binding motifs. Our data suggest that induction of a prooxidant state is crucial for the activation of NF-kappa B by MHBst and **HBx** and might be related to the hepatocarcinogenic potential of the viral proteins. MHBst had a subcellular localization unusual for a viral transactivator: it appeared to be an integral membrane protein of the endoplasmic reticulum.

L66 ANSWER 24 OF 26 HCAPLUS COPYRIGHT 2002 ACS
AB Constructs expressing the core, surface, X, or polymerase proteins of hepatitis B virus were transfected into human cells. In transient assays,

only the polymerase inhibited the responses to interferons .alpha. and .gamma. (IFN-.alpha. and -.gamma.). Stable expression of the polymerase was achieved in the cell line 2fTGH, which carries an IFN-inducible marker gene, by growth under conditions that select for inhibition of the response to IFN-.alpha., but the clones grew poorly. When expressed alone, the terminal protein domain of the polymerase gene inhibited the response to IFN-.alpha. and the reverse transcriptase plus RNase H domains appeared to be toxic. Clones of cells expressing terminal protein alone, selected for the loss of response to IFN-.alpha., grew normally and had no detectable response to IFN-.alpha., IFN-.gamma., or double-stranded RNA. Binding of IFN-.alpha. to these cells was not impaired but did not lead to activation of the E.alpha. subunit of the IFN-induced transcription factor E. These observations are of potential importance in relation to the pathogenesis of chronic hepatitis B virus infection and the resistance of such infection to IFN-.alpha. therapy.

L66 ANSWER 25 OF 26 HCAPLUS COPYRIGHT 2002 ACS
AB The X protein of hepatitis B virus (HBV) has been shown to be a trans-activator for viral and cellular genes. Amino acid sequences in X protein were found to be highly homologous to functionally essential sequences in the Kunitz domain, characteristic of Kunitz-type serine protease inhibitors. Mutations at these sequences completely abolished trans-activation. Consequently, **HBV** X protein resembles a serine protease **inhibitor** or its analog, and may bring about trans-activation by activating certain transcriptional factors through proteolytic cleavage alteration.

L66 ANSWER 26 OF 26 HCAPLUS COPYRIGHT 2002 ACS
AB The chloramphenicol acetyltransferase (cat) gene expression system was used to study the effect of the X protein of hepatitis B virus (HBV) on viral enhancers. Plasmids contg. the HBV enhancer and the core gene promoter linked to the cat gene were cotransfected with a plasmid contg. the X gene into the human hepatoma cell line PLC-PRF/5. The transfected X gene caused a trans-activation of the HBV enhancer. If a frameshift mutation or a deletion in the X structural gene was created, this trans-activation function was abolished. This result and the observation that the frameshift mutation did not alter the transcription of X mRNA suggest that the X protein is the trans-activating factor. The X protein was also capable of trans-activating the simian virus 40 (SV40) and Rous sarcoma virus enhancers (pSV2cat and pRSVcat) in CV-1 cells. However, trans-activation of the SV40 enhancer by the X protein was not obsd. in COS-1 cells. By cotransfecting pSV2cat and the X gene with a plasmid contg. either the intact SV40 genome, the SV40 genome devoid of the T-antigen (T-ag) gene, or only the T-ag gene, it was demonstrated that SV 0 T-ag can suppress trans-activation by the X protein. SV40 T-ag did not inhibit expression of the X gene or inactivate the X protein. The most probable mechanism of this inhibition is that T-ag competes with the X protein for a common target.

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FILE 'CANCERLIT'
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FILE 'EMBASE'
L111        165 L72 AND L85 AND L98

FILE 'HCAPLUS'
L112        197 L73 AND L86 AND L99

FILE 'NTIS'
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FILE 'ESBIOBASE'
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FILE 'BIOTECHNO'
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FILE 'LIFESCI'
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FILE 'HCAPLUS'
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FILE 'BIOTECHNO'
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FILE 'WPIDS'
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L129         0 L77 AND L90(5A)L103

FILE 'CANCERLIT'
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L133      8179 HBV OR HBX

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           167 HBX
L134      3977 HBV OR HBX

FILE 'BIOTECHDS'
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             6 HBX
L135       403 HBV OR HBX

FILE 'BIOSIS'
         10202 HBV
           285 HBX
L136     10342 HBV OR HBX

FILE 'EMBASE'
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           217 HBX
L137      8485 HBV OR HBX

FILE 'HCAPLUS'
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L139       102 HBV OR HBX

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           550 HBV
            10 HBX
L142       557 HBV OR HBX

FILE 'CANCERLIT'
          3085 HBV
           138 HBX
L143      3142 HBV OR HBX

TOTAL FOR ALL FILES
L144     57154 HBV OR HBX

=> s l79 and l144
FILE 'MEDLINE'
L145        12 L67 AND L132

FILE 'SCISEARCH'
L146         9 L68 AND L133

FILE 'LIFESCI'
L147         7 L69 AND L134

FILE 'BIOTECHDS'
L148         0 L70 AND L135

FILE 'BIOSIS'
L149        12 L71 AND L136

FILE 'EMBASE'
L150         8 L72 AND L137

FILE 'HCAPLUS'
L151        11 L73 AND L138

FILE 'NTIS'
L152         0 L74 AND L139

FILE 'ESBIOBASE'
L153         7 L75 AND L140
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FILE 'BIOTECHNO'
L154          7 L76 AND L141

FILE 'WPIDS'
L155          2 L77 AND L142

FILE 'CANCERLIT'
L156          5 L78 AND L143

TOTAL FOR ALL FILES
L157         80 L79 AND L144

=> s (l131 or l157) and py=<1998 range=2001,
FILE 'MEDLINE'
'2001,' IS NOT A VALID RANGE FOR FILE 'MEDLINE'
SEARCH ENDED BY USER

FILE 'SCISEARCH'
            296 PY=<1998
L158          0 (L120 OR L146) AND PY=<1998

FILE 'LIFESCI'
           1632 PY=<1998
L159          0 (L121 OR L147) AND PY=<1998

FILE 'BIOTECHDS'
              8 PY=<1998
                  (PY=<1998)
L160          0 (L122 OR L148) AND PY=<1998

FILE 'BIOSIS'
          70743 PY=<1998
L161          0 (L123 OR L149) AND PY=<1998

FILE 'EMBASE'
             80 PY=<1998
L162          0 (L124 OR L150) AND PY=<1998

FILE 'HCAPLUS'
           5094 PY=<1998
L163          0 (L125 OR L151) AND PY=<1998

FILE 'NTIS'
           7603 PY=<1998
L164          0 (L126 OR L152) AND PY=<1998

FILE 'ESBIOBASE'
            178 PY=<1998
L165          0 (L127 OR L153) AND PY=<1998

FILE 'BIOTECHNO'
        1165526 PY=<1998
L166         27 (L128 OR L154) AND PY=<1998

FILE 'WPIDS'
          10388 PY=<1998
                  (PY=<1998)
L167          0 (L129 OR L155) AND PY=<1998
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FILE 'CANCERLIT'
           562 PY=<1998
L168         0 (L130 OR L156) AND PY=<1998

TOTAL FOR ALL FILES
L169        27 (L131 OR L157) AND PY=<1998

=> fil medl
COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                     132.24     132.39

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)            SINCE FILE      TOTAL
                                                         ENTRY    SESSION
CA SUBSCRIBER PRICE                                      -9.91      -9.91

FILE 'MEDLINE' ENTERED AT 10:57:41 ON 13 MAR 2002

 => s (l131 or l157) and py=<1998 range=2001000000,
         72633 PY=<1998
L170         0 (L119 OR L145) AND PY=<1998

=> log y
COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.32     132.71

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)            SINCE FILE      TOTAL
                                                         ENTRY    SESSION
CA SUBSCRIBER PRICE                                       0.00      -9.91

STN INTERNATIONAL LOGOFF AT 10:58:08 ON 13 MAR 2002


Connection closed by remote host
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